

# Midwest RCE Aerosol Biology and Small Animals Core



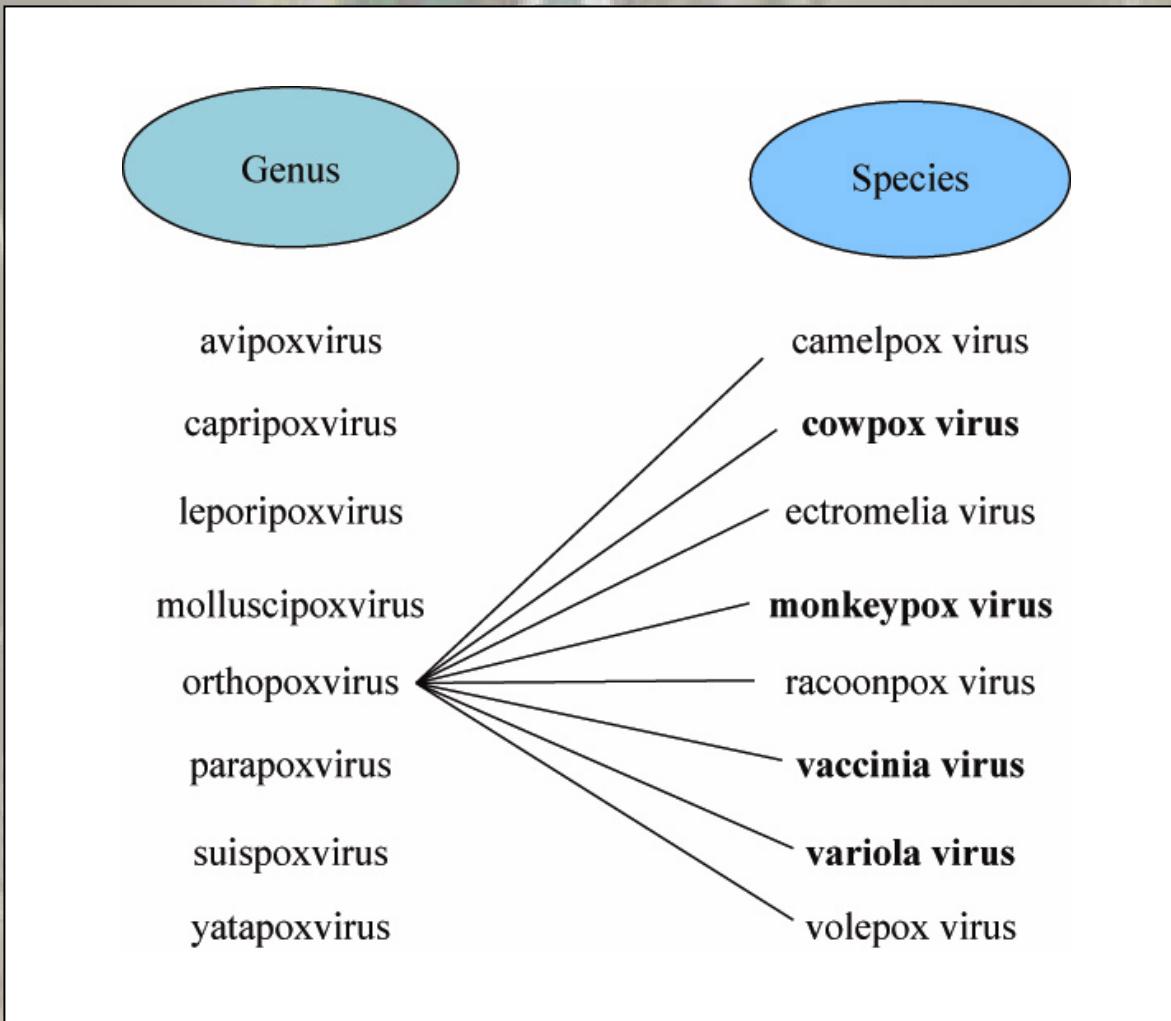
# Regional Partners



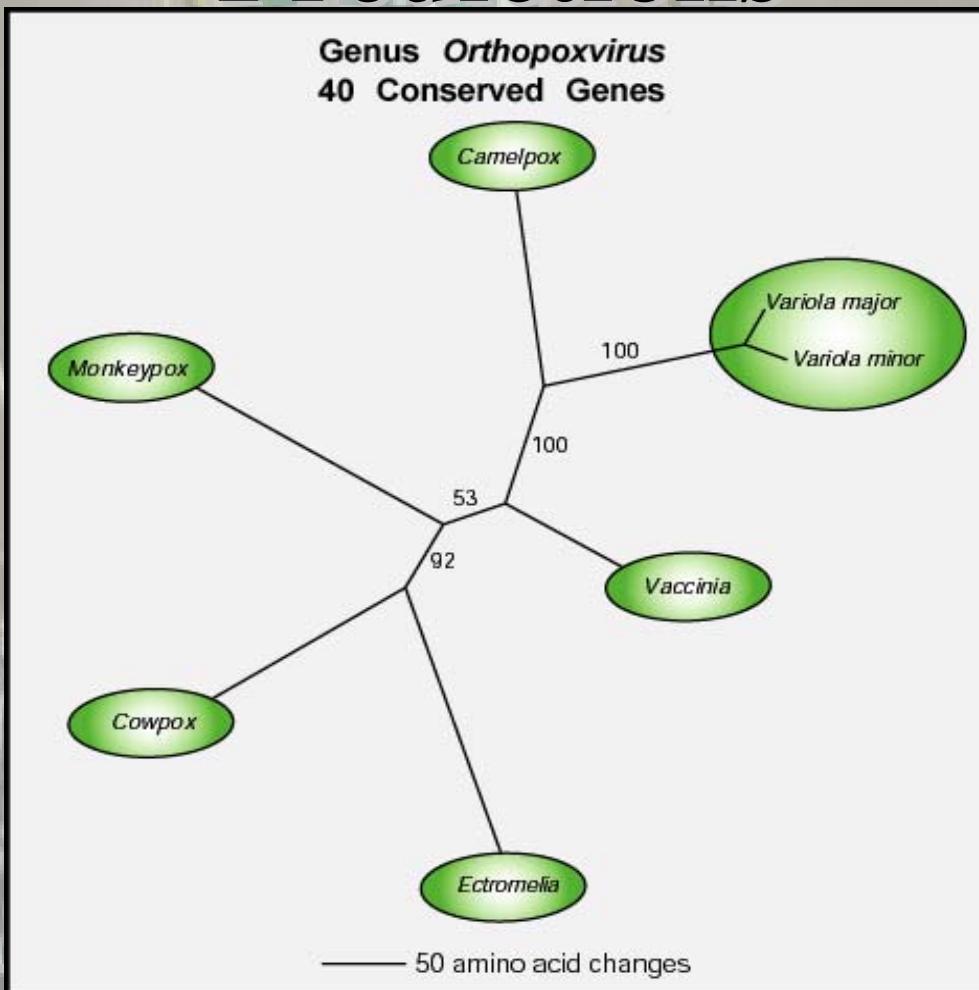
# Mission

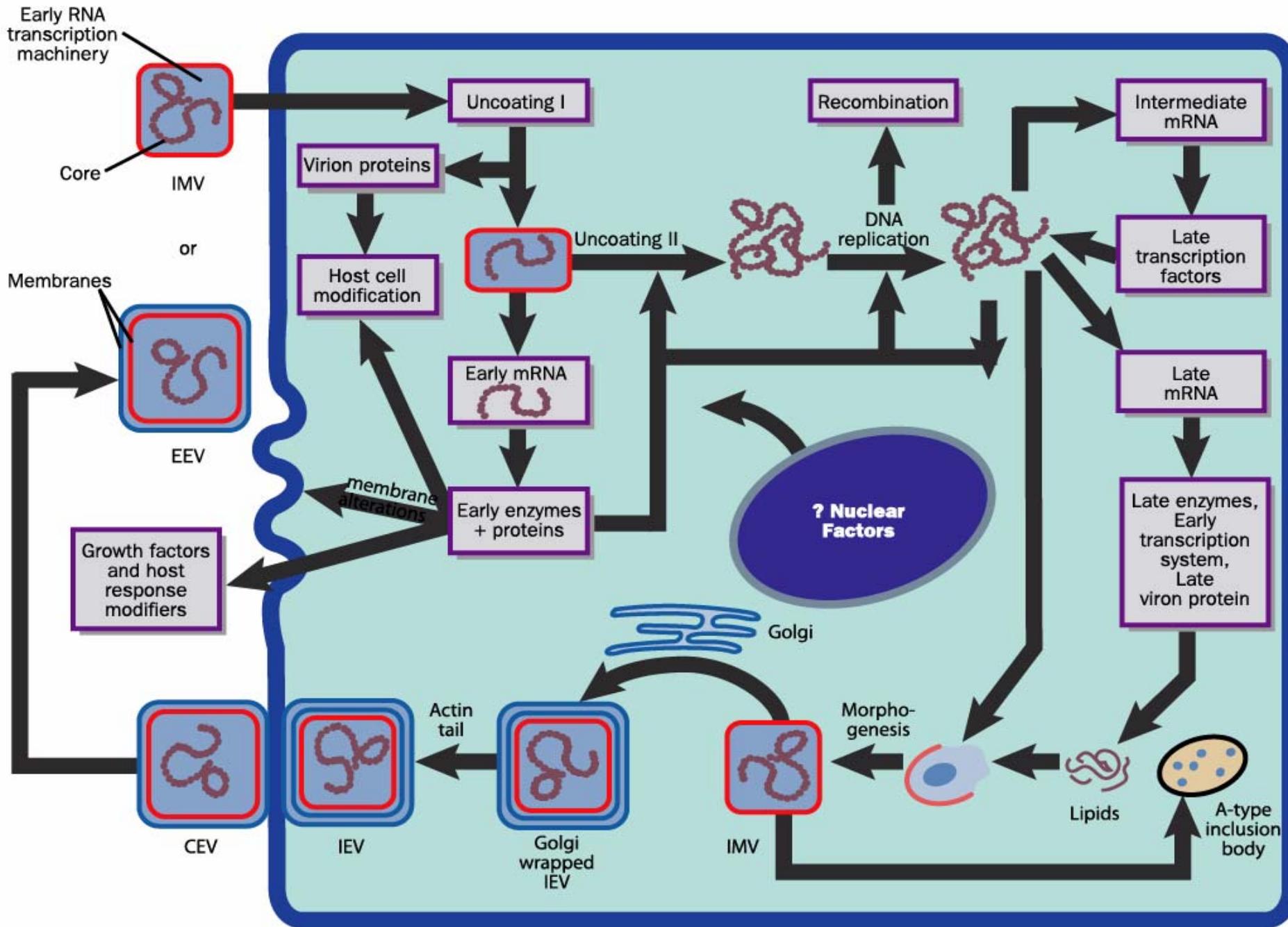
- Provide respiratory tract challenges for development of therapeutics and vaccines against smallpox and pneumonic plague
- Evaluate the delivery of therapeutics to the respiratory tract to study early intervention strategies
- Use the ectromelia model for the study of innate and acquired immunity to poxviruses
- Develop approaches for inactivation of bioparticles in the air

# Poxvirus Taxonomy

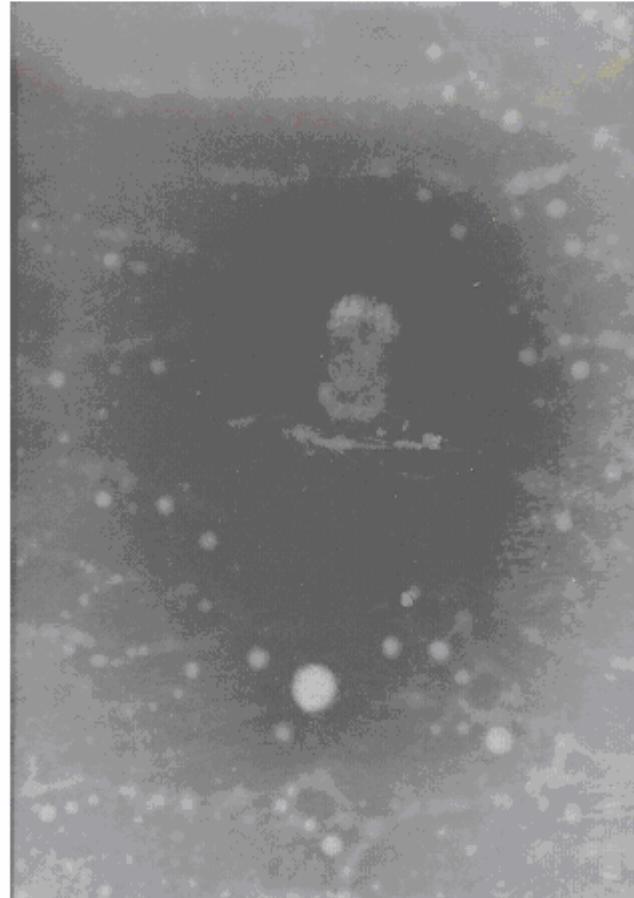


# Orthopoxvirus Phylogenetic Predictions



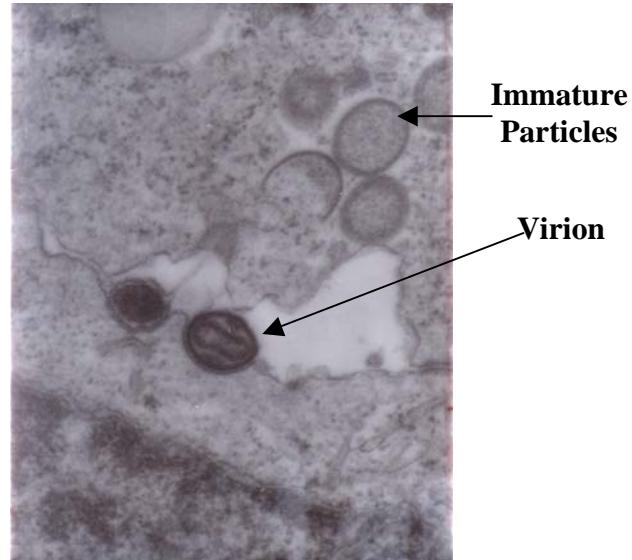


# Negative-Stained Virion

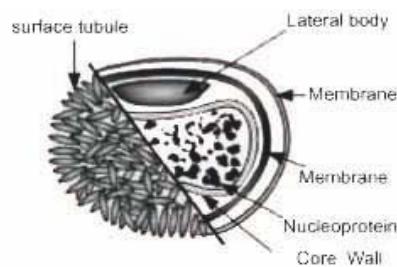


# Thin-section of Cowpox Virion

A



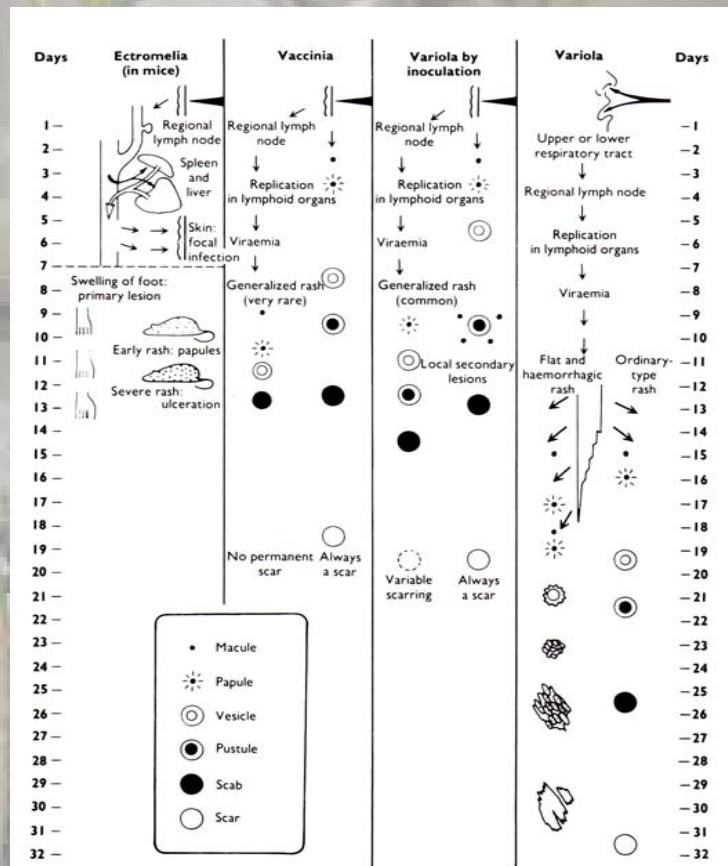
B



# Small Animal Models for Poxvirus Respiratory Infection

- Cowpox virus  $LD_{50} \sim 10^4$  PFU
- Ectromelia virus  $LD_{50} < 50$  PFU
- Monkeypox virus limited models
- Vaccinia virus  $LD_{50} \sim 10^5$

# Pathogenesis of orthopoxvirus



# Routes of Infection

- Intratracheal
- Intranasal
- Aerosol

# Intranasal Ectromelia Virus Infection of A/NCR mice

Virus Dose (PFU/mouse) <sup>1</sup>	Mean time to Death	Mortality rate	LD <sub>50</sub> <sup>2</sup> (PFU)
5,000	7±0.0	100%	
500	7.3±0.5	100%	
50	8±0.0	100%	
5.0	9±0.0	100%	0.3
0.5	10±1.4	50%	
0.05	10	25%	

<sup>1</sup>Experiment C-97

<sup>2</sup>Reed and Muench

# Aerosol Ectromelia Virus Infection of A/NCR mice

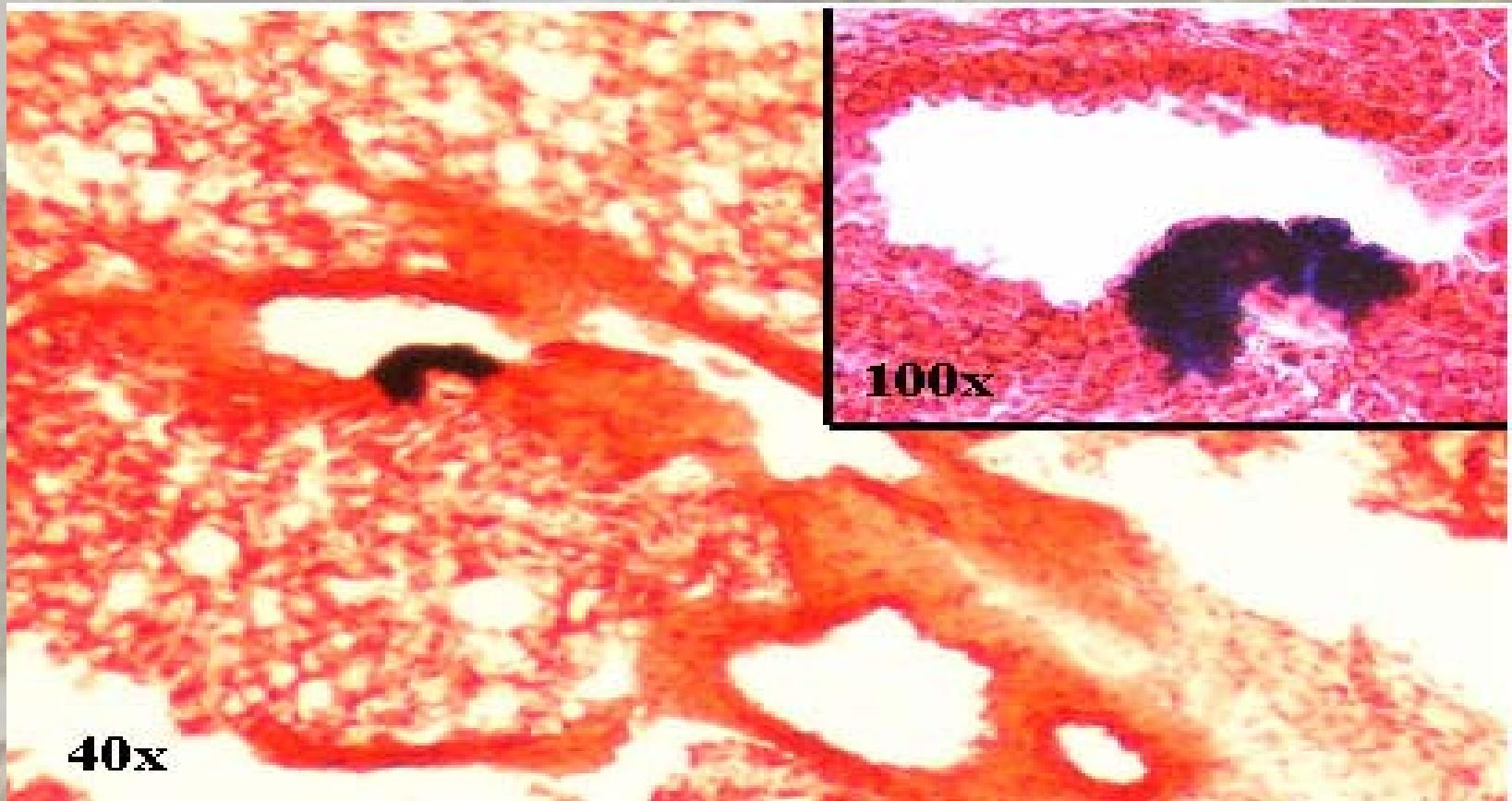
Presented Dose (PFU/mouse) <sup>1</sup>	Mean time to Death	Mortality rate	LD <sub>50</sub> <sup>2</sup> (PFU)	Seroconversion of survivors at T=21 days pi
1.9 x 10 <sup>4</sup>	8.1±0.4	100%		N/A <sup>3</sup>
1.3 x 10 <sup>3</sup>	9.3±0.5	100%		N/A
63	10.2±1.3	67%	32	1/3
6.3	14	9%		0/7
0	N/A	0%		0/8

<sup>1</sup>Experiment C-78

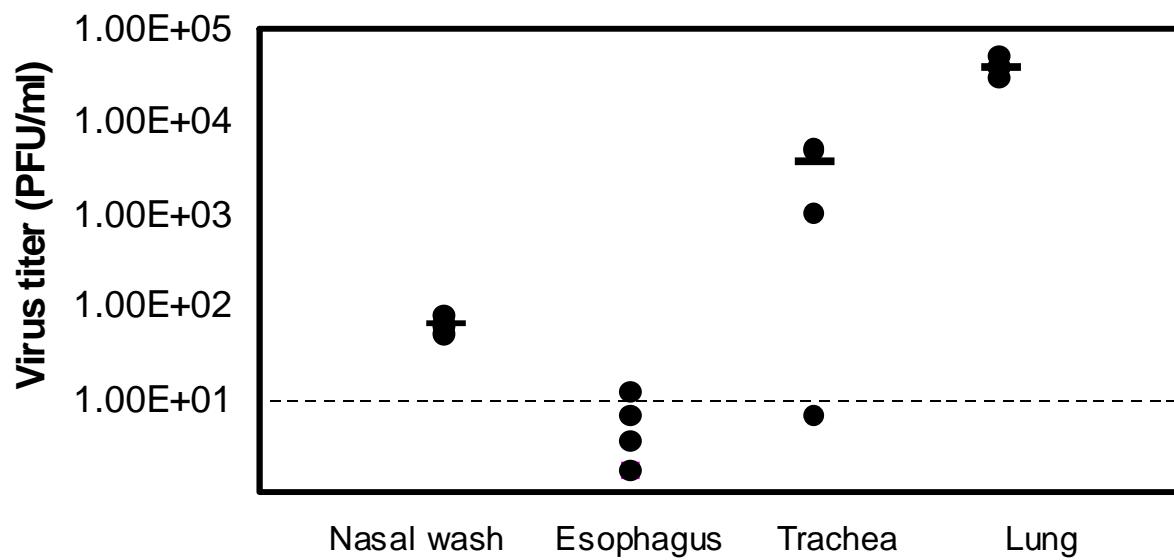
<sup>2</sup>Reed and Muench

<sup>3</sup>not applicable

# Ectromelia Virus Focus of Infection in the Mouse Lung



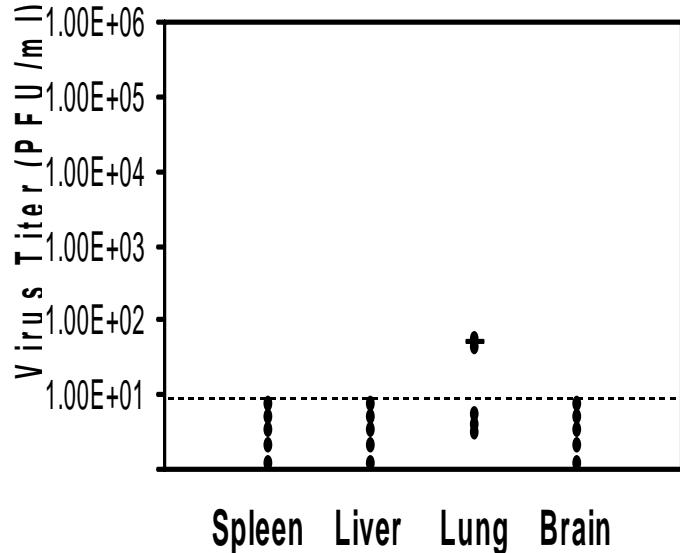
# Tissue Infectivity Following Aerosol Infection



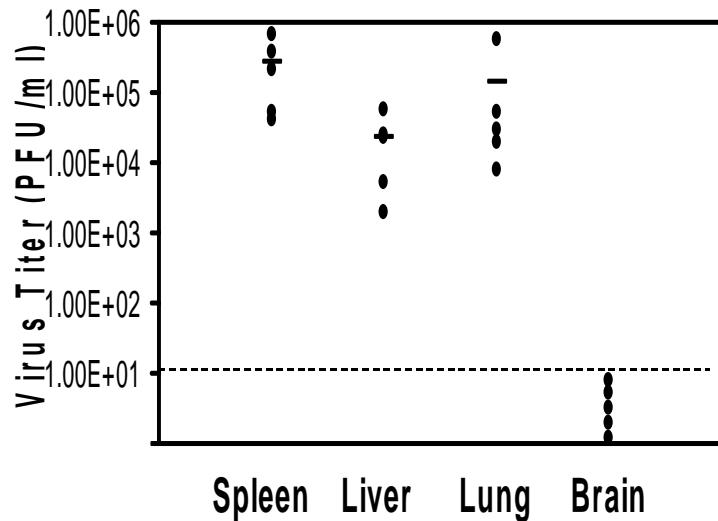
Presented aerosol dose  $1.6 \times 10^4$  PFU ( $1000 LD_{50}$ ), C-90

# Low Dose Ectromelia Virus Aerosol Challenge of Vaccinated Mice

Dryvax Vaccinated mice



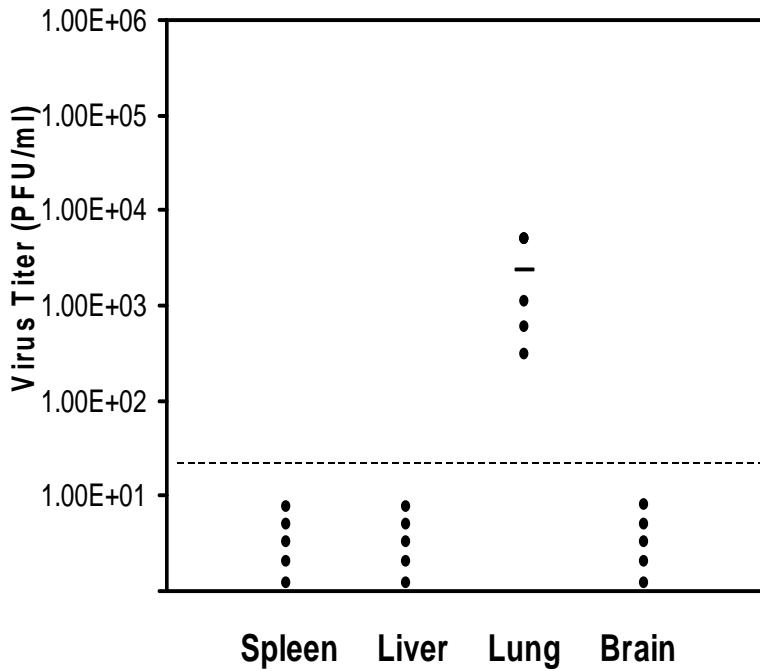
Control Mice



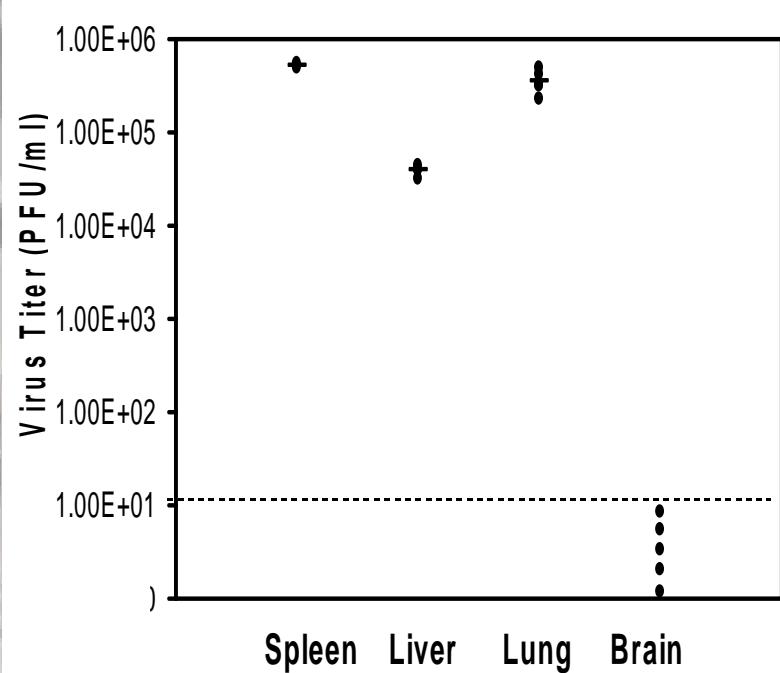
Presented aerosol dose  $7.3 \times 10^3$  PFU (200 LD<sub>50</sub>)

# High Dose Ectromelia Virus Aerosol Challenge of vaccinated mice

Dryvax Vaccinated Mice



Control Mice



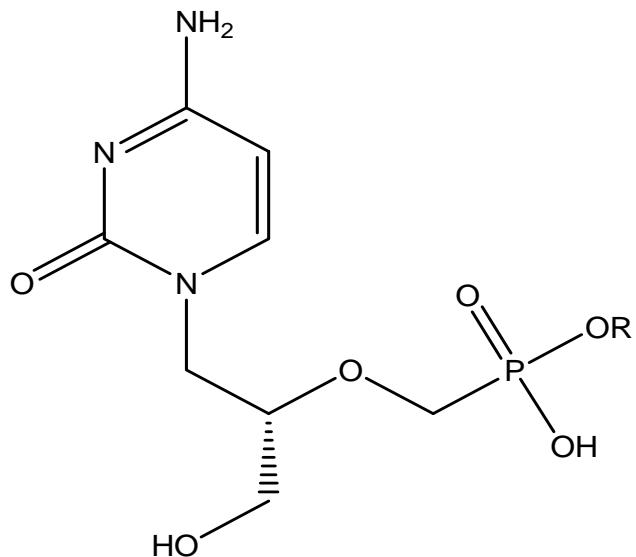
Presented aerosol dose  $3.4 \times 10^4$  PFU ( $1000 \text{ LD}_{50}$ )

# Aerosolized Cidofovir Treatment of an Aerosol Cowpox Virus Infection

Mean Aerosol Dose and wt	Aerosol Cidofovir			Subcutaneous Cidofov		
	Day Treated	Dose (mg/kg)	Survival	Day Treated	Dose (mg/kg)	Survival
$5.4 \times 10^5$ PFU/ 8.9 g	0	0.5-5	10/10*	0	25	7/10*
	1	0.5-5	9/10*	1	25	6/10*
	2	0.5-5	5/10*	2	25	5/10*
	Placebo	N/A	0/8			

From: M. Bray Antiviral Research 54 (2002) 1219-142

# Structure of Cidofovir and Ether Lipid Esters



R =

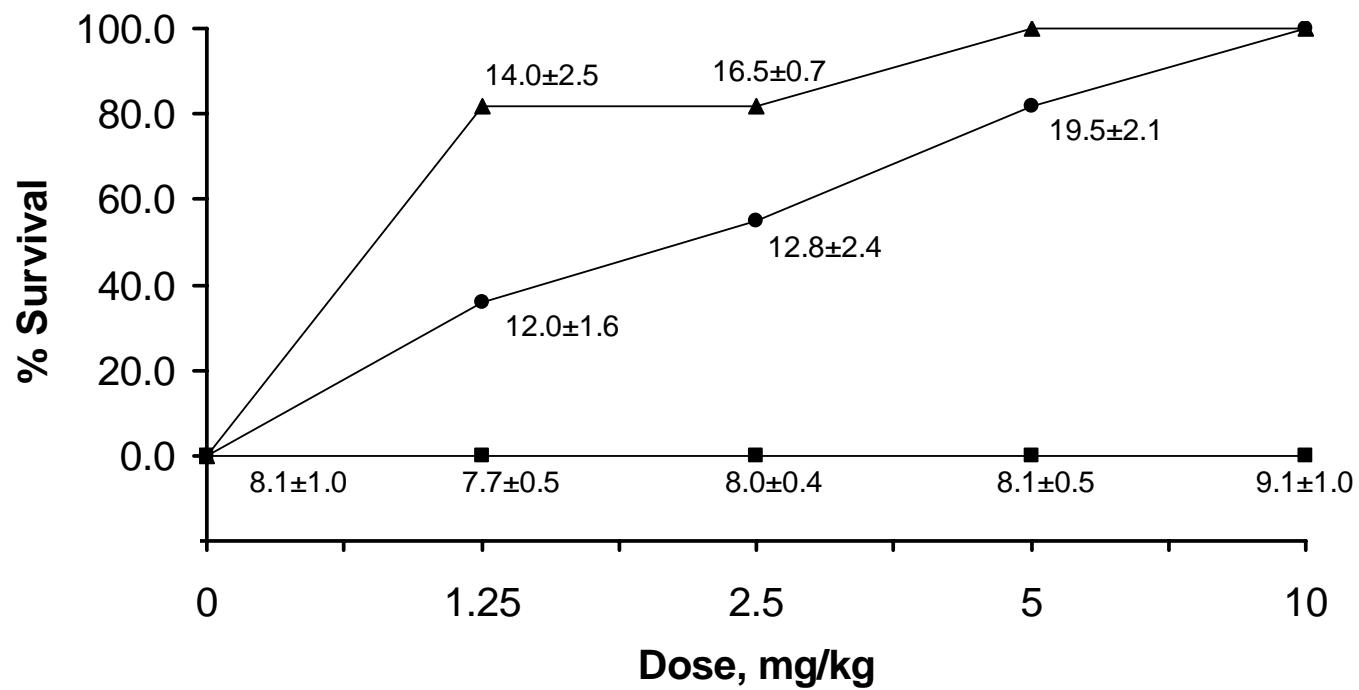
- H
- $\text{CH}_3(\text{CH}_2)_{15}\text{O}(\text{CH}_2)_3$
- $\text{CH}_3(\text{CH}_2)_{17}\text{O}(\text{CH}_2)_2$
- $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_8\text{O}(\text{CH}_2)_2$
- $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_8\text{O}(\text{CH}_2)_3$

compound

cidofovir  
hexadecyloxypropyl cidofovir, HDP-CDV  
octadecyloxyethyl cidofovir, ODE-CDV  
oleyloxyethyl cidofovir, OLE-CDV  
oleyloxypropyl cidofovir, OLP-CDV

# Efficacy of HDP-CDV and ODE-CDV

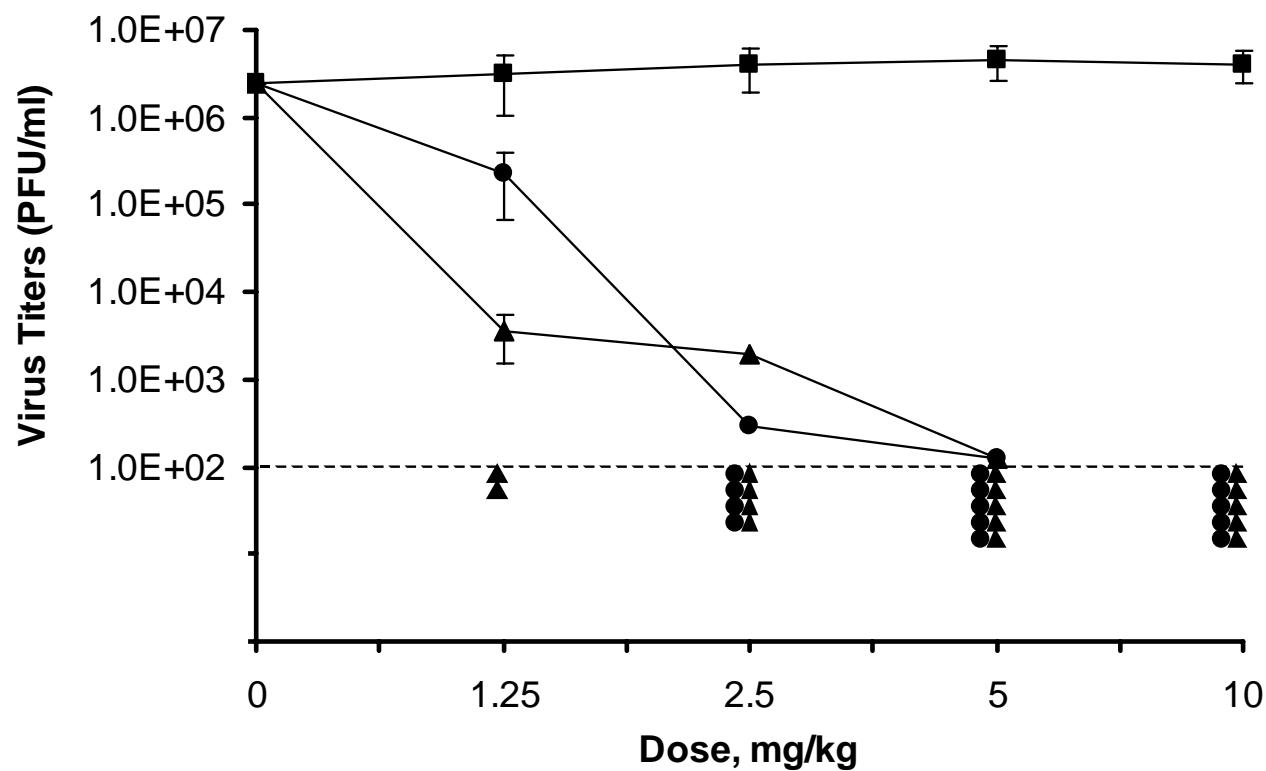
## Survival



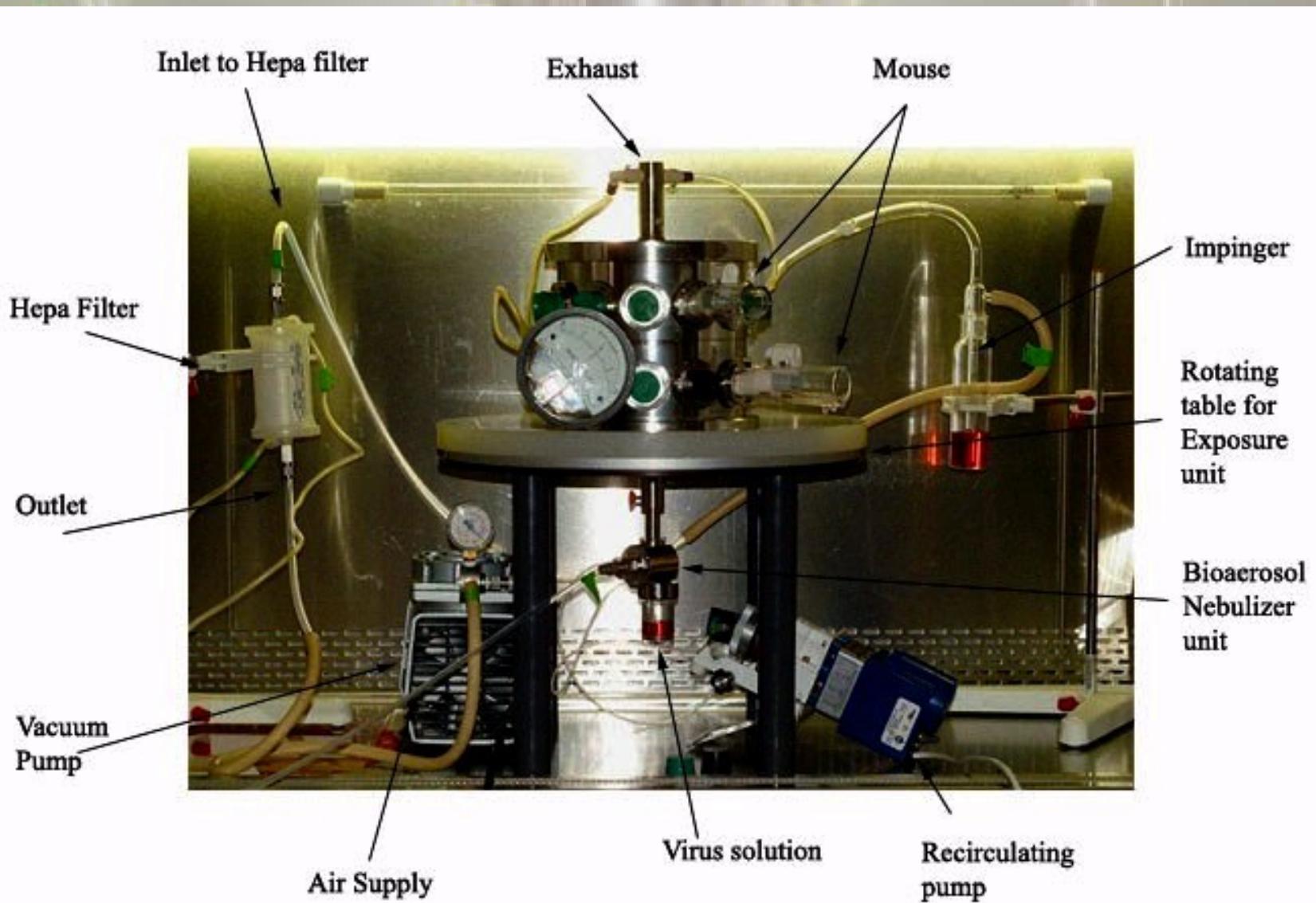
Presented aerosol dose  $1.3 \times 10^3$  PFU (50 LD<sub>50</sub>) C-50/52

# Efficacy of HDP-CDV and ODE-CDV

## Liver Titers



# Nose-only Inhalation Exposure System





# Collaborators

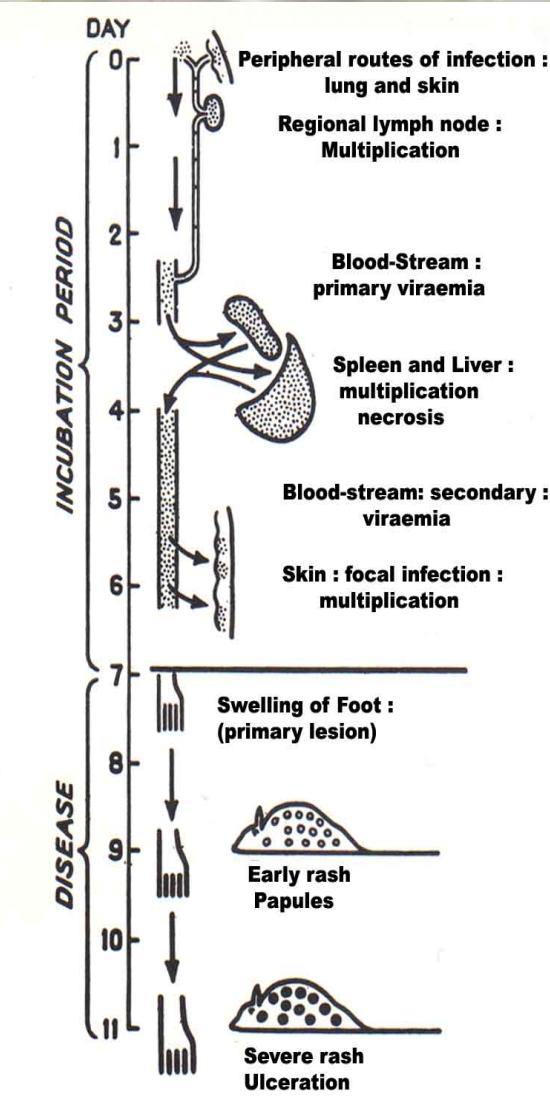
## Saint Louis University      Washington University

- Jill Schriewer
- Gelita Owens
- Mark Buller
- Roger Lewis
- Chad Roy

- Pratim Biswas
- Da-Ren Chen
- Myong-Hwa Lee

Initial Funding from an Antiviral contract with NIAID

# Mousepox



# Tissue Infectivity Following Intranasal Infection

